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Synthesis of allylic trifluoromethyl alcohols from 1-trifluoromethyl-epoxy ethers

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Abstract

α-Thiophenyl ketones are easily available by the regioselective ring-opening of 1-trifluoromethyl-epoxy ethers with phenyl sodium thiolate. Their in situ reduction with $NaBH_4$, followed by oxidation with $NaIO_4$ and thermal decomposition of the resultant sulphoxides, provided allylic trifluoromethyl alcohols in high overall yield.

Keywords: Synthesis; Allylic trifluoromethyl alcohols; Epoxy ethers; α-Thiophenyl ketones; NMR spectroscopy

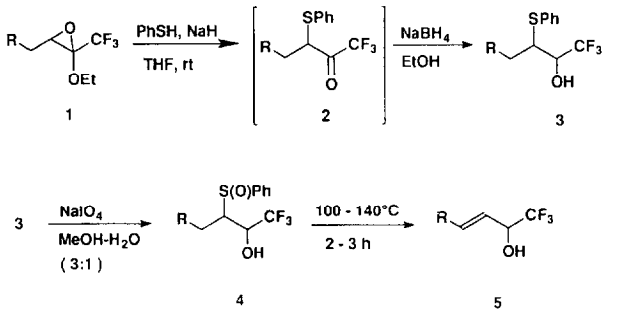
1. Introduction

Allylic trifluoromethyl alcohols could be versatile building blocks for the synthesis of CF_3-containing compounds. Several methods for their preparation have been described: the reaction under ultrasonic irradiation of an organozinc reagent with trifluoroacetaldehyde [1]; the double reduction of trifluoromethyl alkynyl ketones [2]; direct trifluoromethylation of appropriate ketones or aldehydes [3]. Two peculiar cases have been described from trifluoromethyl epoxides: the abstraction by LDA of an active proton in the β-position to the oxirane ring [4] and the reaction of the (*S*)-3,3,3-trifluoropropene oxide with triphenylphosphine followed by the condensation of the resulting phosphonium salt with an aldehyde [5].

We report here a practical and general multigram-scale synthetic method for the preparation of allylic trifluoromethyl alcohols through a thermal elimination of β-CF_3 from β-hydroxy sulphoxides [6], prepared in two steps from 1-trifluoromethyl-epoxy ethers.

2. Results and discussion

Allylic trifluoromethyl alcohols were prepared from epoxy ethers **1** (Scheme 1), easily available from trifluoroacetic acid [7]. The regioselective opening of **1** with sodium thiophenate smoothly proceeded (10 min at room temperature) to give α-thiophenyl ketones **2** [8], which were reduced in situ with $NaBH_4$. β-Thiophenyl alcohols **3** were isolated in good yield from **1** (Table 1). The reduction is stereoselective leading to the *syn* isomer as the major product. This *syn* configuration has been deduced from ^{19}F NMR chemical shifts: for α-functionalized alcohols, $|\delta(^{19}F)|$ is larger for the *syn* than for the *anti* diastereoisomer[1].



Scheme 1.

Reaction of β-hydroxy sulphides **3** with $NaIO_4$ led to β-hydroxy sulphoxides **4** (Table 2), which were converted to allylic alcohols **5** in high yield by heating the neat compounds for several hours at 80–140 °C (Table 3).

This method of preparation of allylic trifluoromethyl alcohols offers the advantage of being practical on a large scale,

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[1] This empirical rule was based on the data for α-bromo [9], α-azido [10], α-amino [11] and α-peptidyl alcohols [10]; no exceptions are known.

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Table 1
Preparation of thiophenyl alcohols **3** from epoxides **1**

Entry No.	Thiophenyl alcohol **3**	R	Yield (%)
1	**3a**	cyclohexyl	77
2	**3b**	*p*-MeO-C_6H_4-CH_2	71
3	**3c**	n-pentyl	78
4	**3d**	C_6H_5	71
5	**3e**	C_6H_5-CH_2	76

Table 2
Preparation of sulphoxides **4** from thiophenyl alcohols **3**

Entry No.	Sulphoxide **4**	R	Yield (%)
1	**4a**	Cyclohexyl	90
2	**4b**	*p*-Meo-C_6H_4-CH_2	93
3	**4c**	n-Pentyl	90
4	**4d**	C_6H_5	55 [a]
5	**4e**	C_6H_5-CH_2	87

[a] Formation of **4d** was accompanied by allylic alcohol **5d**, isolated in 43% yield.

using cheap starting materials, easy-to-handle reagents and technically simple procedures.

3. Experimental details

3.1. General

^{19}F NMR, ^1H NMR and ^{13}C NMR spectra were recorded on a 200 MHz multinuclear spectrometer. ^{19}F NMR spectra are referenced with external $CFCl_3$, and ^1H NMR and ^{13}C NMR spectra with tetramethylsilane. Multiplicities described in the ^{13}C NMR data are for J_{CF} coupling. In all NMR measurements, $CDCl_3$ was used as solvent. GC analyses were performed using an SE 30 capillary column (25 m).

3.2. Materials

THF was purified by distillation from sodium ketyl. All reactions with NaH were performed in oven-dried apparatus. NaH was washed with pentane from a suspension in mineral oil obtained from Fluka Co.

3.3. Preparation of thiophenyl alcohols 3: typical procedure for 1,1,1-trifluoro-2-hydroxy-3-S-phenyl-nonane (3c)

Sodium hydride (300 mg, 80% dispersion in oil, 10 mmol) was placed in an argon-flushed three-necked flask and washed twice with dry pentane, after which THF (50 ml) was added via a syringe through a septum cap. The suspension was cooled to 0 °C and PhSH (1.03 ml, 10 mmol) was added dropwise. The mixture was stirred for ca. 0.5 h at room temperature and epoxy ether **2c** (2.54 g, 9 mmol) then added in one portion to the suspension of sodium thiophenate. After 10 min the precipitate disappeared. The reaction mixture was quenched with an aqueous solution of NH_4Cl and extracted twice with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. Ethanol (20 ml) was added and the solution obtained cooled to 0 °C. $NaBH_4$ (0.76 g, 20 mmol) was added in portions over 15 min and the reaction mixture then stirred at room temperature for 2 h. NH_4Cl (saturated aq. solution, 20 ml) was added at 0 °C and the mixture extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography on silica gel (eluent pentane/ether 20:1, 5:1) to afford 2.49 g (78%) of **3c** as a mixture of *syn* and *anti* isomers (ratio 91:9).

^1H NMR δ: 0.91 (t, J=7.0 Hz, 3H); 1.33 (b s, 6H); 1.65 (m, 4H); 2.82 (d, J=8.0 Hz, 1H, O*H*, *anti*); 3.32 (dt, J=7.0 and 6.7 Hz, 1H); 3.41 (d, J=7.5 Hz, 1H, O*H*, *syn*); 3.85 (ddq, J=7.0, 7.5 and 7.1 Hz, 1H); 7.35 (m, 3H); 7.5 (m, 2H) ppm. ^{13}C NMR δ: 14.1, 22.7, 27.1, 28.9, 31.7, 32.4, 46.1 and 52.2, 71.9 (q, ^2J=30 Hz, *C*–CF_3); 124.8 (q, ^1J=292 Hz, CF_3); 128.3; 129.3; 133.2 ppm ^{19}F NMR δ: −75.4 (d, J=7.1 Hz) (*syn*); −74.5 (d, J=7.5 Hz) (*anti*) ppm.

1,1,1-Trifluoro-2-hydroxy-3-*S*-phenyl-4-cyclohexyl-2-butane (**3a**) was obtained according to the above typical procedure in 77% yield as a mixture of *syn* and *anti* isomers (ratio 93:7).

^1H NMR δ: 0.71–1.75 (m, 13H); 2.69 (d, J=7.9 Hz, 1H, O*H*, *anti*); 3.31 (d, J=7.5 Hz, 1H, O*H*, *syn*); 3.85 (ddq, J=7.0, 7.5, 6.8 Hz, 1H); 7.27–7.44 (m, 5H) ppm. ^{13}C NMR δ: 25.9, 26.2, 26.4, 32.2, 33.6, 34.7, 39.5, 45.6 and 49.0, 71.4 (q, ^2J=30 Hz *C*–CF_3); 121.8, 125.1 (q, ^1J=293 Hz, CF_3); 128.2; 129.1; 129.4; 131.8; 133.3 ppm. ^{19}F NMR δ: −75.0 (d, J=6.8 Hz) (*syn*); −74.4 (d, J=7.4 Hz) (*anti*) ppm.

1,1,1-Trifluoro-2-hydroxy-3-*S*-phenyl-5-(4-methoxy)-phenyl-propane (**3b**) was obtained according to the above

Table 3
Preparation of allylic alcohols **5** from sulphoxides **4**

Entry No.	Alcohol **5**	R	Time (h)	Temp. (°C)	Yield (%)
1	**5a**	Cyclohexyl	2	125-130	91
2	**5b**	*p*-MeO-C_6H_4-CH_2	3	135-140	86
3	**5c**	n-pentyl	3	135-140	81
4	**5d**	C_6H_5	3	100-110	85
5	**5e**	C_6H_5-CH_2	3	125-130	87

typical procedure in 71% yield as a mixture of *syn* and *anti* isomers (ratio 99:1).

^{1}H NMR δ: 1.95 (m, 2H); 2.82 (m, 2H); 3.22 (dt, J=7.0, 6.9 Hz, 1H); 3.32 (d, J=7.6 Hz, 1H, O*H*, *syn*); 3.73 (s, 3H); 3.88 (ddq, J=7.0, 7.6, 7.1 Hz, 1H); 7.79 (m, 2H); 6.98 (m, 2H); 7.31 (m, 3H); 7.38 (m, 2H) ppm. ^{13}C NMR δ: 32.0, 33.7, 50.7 and 55.1, 65.6, 71.7 (q, ^2J=29 Hz, *C*–CF_3); 113.8, 124.5 (q, ^1J=284 Hz, CF_3); 128.0; 129.0; 129.2; 131.9; 132.3; 132.7; 158.0 ppm. ^{19}F NMR δ: −75.3 (d, J=7.0 Hz) (*syn*) ppm.

1,1,1-Trifluoro-2-hydroxy-3-*S*-phenyl-4-phenyl-butane (**3d**) was obtained according to the above typical procedure in 71% yield as a mixture of *syn* and *anti* isomers (ratio 97:3).

^{1}H NMR δ: 2.83 (ddd, J=8.2, 7.6, 13.5 Hz, 1H); 2.92 (d, J=8.6 Hz, 1H, O*H*, *syn*); 3.41 (dt, J=3.3, 7.9 Hz, 1H); 4.15 (ddq, J=3.3, 7.0, 8.6 Hz, 1H); 7.15–7.51 (m, 10H) ppm. ^{13}C NMR δ: 39.2, 45.4 and 52.7, 70.5 (q, ^2J=31 Hz, *C*–CF_3); 124.8 (q, ^1J=283 Hz, CF_3); 127.0; 127.3; 128.1; 128.7; 129.1; 129.3; 132.7; 133.1; 137.7 ppm. ^{19}F NMR δ: −75.5 (d, J=7.0 Hz) (*syn*) ppm.

1,1,1-Trifluoro-2-hydroxy-3-*S*-phenyl-5-phenyl-pentane (**3e**) was obtained according to the above typical procedure in 76% yield as a mixture of *syn* and *anti* isomers (ratio 91:9).

^{1}H NMR δ: 1.92 (m, 1H); 2.15 (m, 1H); 2.98 (m, 2H); 3.32 (m, 1H); 3.51 (d, J=7.9 Hz, 1H, O*H*, *syn*); 3.92 (ddq, J=6.8, 7.9, 2.0 Hz, 1H); 7.15–7.57 (m, 10H) ppm. ^{13}C NMR δ: 33.2, 33.6, 45.6 and 51.0, 71.5 (q, ^2J=30 Hz, *C*–CF_3); 124.5 (q, ^1J=283 Hz, CF_3); 126.0; 126.3; 128.2; 128.4; 128.5; 129.2; 131.8; 133.0; 140.4 ppm. ^{19}F NMR δ: −75.2 (d, J=6.8 Hz) (*syn*); −74.6 (d, J=7.4 Hz) (*anti*) ppm.

3.4. Preparation of sulphoxides 4: typical procedure for 1,1,1-trifluoro-2-hydroxy-3-(phenylsulphinyl)-4-cyclohexyl-2-butane (4a)

To a solution of thio alcohol **3a** (3.18 g, 10 mmol) in MeOH (100 ml) was added in one portion $NaIO_4$ (2.27 g, 10.5 mmol) in H_2O (35 ml) with stirring. The reaction mixture was heated at 70 °C for 4 h (control by TLC), cooled and extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography on silica gel (eluent pentane/ether 5:1, 1:1) to afford the sulphoxide **4a** (3.01 g, 90%). All sulphoxides **4** were obtained as a mixture of diastereoisomers in a ratio approximately 45:45:5:5. The NMR data described below concern the two major isomers.

^{1}H NMR δ: 0.71–1.75 (m, 13H); 2.92 (dt, J=4.6, 7.2 Hz); 3.19 (dt, J=5.8, 6.0 Hz, 1H, *H*-3); 4.21, 4.37 (m, 1H, *H*-2); 5.18 (d, J=5.1 Hz); 5.82 (d, J=6.0 Hz, 1H, O*H*); 7.55 (m, 4H); 7.58 (m, 1H) ppm. ^{13}C NMR δ: 25.6 and 25.7, 25.8 and 26.0, 28.6, 31.8 and 32.0, 32.5 and 32.6, 34.5 and 34.8, 61.1 and 62.1, 70.5 (q, ^2J=32 Hz, *C*–CF_3); 124.5, 124.7 (q, ^1J=283 Hz, CF_3); 124.3 and 125.6, 129.1, 131.0 and 131.7, 140.1 and 141.1 ppm. ^{19}F NMR δ: −74.6 (d, J=6.2 Hz); −75.8 (d, J=6.0 Hz) ppm.

1,1,1-Trifluoro-2-hydroxy-3-(phenylsulphinyl)-5-(4-methoxy)phenyl-propane (**4b**) was obtained according to the above typical procedure in 93% yield as a mixture of diastereoisomers.

^{1}H NMR δ: 1.92 (m, 2H); 2.12 (m, 1H); 2.55 (m, 1H); 2.77, 3.12 (m, 1H, *H*-3); 3.72 (s, 3H); 3.75 (s, 3H); 4.35, 4.55 (m, 1H, *H*-2); 5.21 (d, J=5.5 Hz); 5.81 (d, J=7.0 Hz, 1H, O*H*); 6.65 (m, 2H); 6.72 (m, 1H); 6.89 (m, 1H); 7.51 (m, 4H); 7.55 (m, 1H) ppm. ^{19}F NMR δ: −75.0 (d, J=7.3 Hz); −76.0 (d, J=7.5 Hz) ppm.

1,1,1-Trifluoro-2-hydroxy-3-(phenylsulphinyl)-nonane (**4c**) was obtained according to the above typical procedure in 90% yield as a mixture of diastereoisomers.

^{1}H NMR δ: 0.91 (m, 3H); 1.33 (m, 8H); 1.67 (m, 2H); 2.82 (dt, J=7.0, 6.9 Hz); 3.12 (dt, J=7.5, 9.0 Hz, 1H, *H*-3); 4.35, 4.55 (m, 1H, *H*-2); 5.38 (d, J=5.5 Hz); 5.99 (d, J=6.5 Hz, 1H, O*H*); 7.49 (m, 4H); 7.6 (m, 1H) ppm. ^{19}F NMR δ: −75.3 (d, J=6.6 Hz, CF_3); 76.2 (d, J=7.4 Hz, CF_3) ppm.

1,1,1-Trifluoro-2-hydroxy-3-(phenylsulphinyl)-4-phenyl-butane (**4d**) was obtained according to the above typical procedure in 55% yield as a mixture of diastereoisomers (alcohol **5d** was also isolated in 43% yield).

^{1}H NMR δ: 2.73, and 3.39 (m, 1H, *H*-C3); 2.98 (m, 2H); 4.15, and 4.39 (m, 1H, *H*-C2); 4.85 (d, J=6.0 Hz); 5.39 (d, J=7.0 Hz, 1H, O*H*); 6.85 (m, 1H); 6.95–7.58 (m, 9H) ppm. ^{19}F NMR δ: −75.5 (d, J=6.7 Hz); −75.9 (d, J=6.7 Hz) ppm.

1,1,1-Trifluoro-2-hydroxy-3-(phenylsulphinyl)-5-phenyl-pentane (**4e**) was obtained according to the above typical procedure in 87% yield as a mixture of diastereoisomers.

^{1}H NMR δ: 1.88 (m, 2H); 2.65 (m, 2H); 2.79, 3.05 (m, 1H, *H*-C3); 4.27, 4.45 (m, 1H, *H*-C2); 5.09 (d, J=6.0 Hz); 5.59 (d, J=7.0 Hz, 1H, O*H*); 6.95 (m, 1H); 7.01–7.29 (m, 4H); 7.31–7.62 (m, 5H) ppm. ^{19}F NMR δ: −74.5 (d, J=5.7 Hz); −75.2 (d, J=7.2 Hz) ppm.

3.5. Preparation of allylic alcohols 5: typical procedure for (E)-1,1,1-trifluoro-2-hydroxy-3-nonene (5c)

Sulphoxide **4c** (1.68 g, 5 mmol) was heated at 135–140 °C for 3 h (control by TLC), cooled and purified by column chromatography on silica gel (eluent pentane ether 10:1, 2:1) to afford 0.85 g (81%) of the allylic alcohol **5c** with traces of the *Z* isomer (GC).

^{1}H NMR δ: 0.91 (t, J=7.5 Hz, 3H); 1.3 (m, 6H); 2.05 (dt, J=7.0, 6.9 Hz, 2H); 2.2 (s, 1H, O*H*); 4.32 (dq, J=7.0, 6.8 Hz, 1H); 5.45 (dd, J=7.0, 14.2 Hz, 1H); 5.92 (dt, J=7.1, 14.2 Hz, 1H) ppm. ^{13}C NMR δ: 13.9, 22.3, 28.2, 31.1, 32.1, 71.5 (q, ^2J= 32 Hz, *C*–CF_3); 121.8, 124.3 (q, ^1J=280 Hz, CF_3); 139.1 ppm. ^{19}F NMR δ: −79.6 (d, J=6.8 Hz) ppm. Analysis: Calc. for $C_9H_{15}OF_3$: C, 55.08; H, 7.72%. Found: C, 55.45; H, 7.89%.

(*E*)-1,1,1-Trifluoro-2-hydroxy-4-cyclohexyl-3-butene (**5a**) was obtained according to the above typical procedure in 91% yield.

^{1}H NMR δ: 0.71–1.38 (m, 4H); 1.48–1.82 (m, 6H); 1.95 (m, 1H); 2.15 (bs, 1H); 4.31 (m, 1H); 5.37 (dd, J=7.0, 15.2 Hz, 1H); 5.85 (dd, J=7.1, 15.2 Hz, 1H) ppm. ^{13}C NMR δ: 25.8, 26.0, 40.3, 71.8 (q, ^2J=32 Hz, *C*–CF_3); 119.8, 124.6 (q, ^1J=281 Hz, CF_3); 144.7 ppm. ^{19}F NMR δ: −79.7 (d, J=6.6 Hz) ppm. Analysis: Calc. for $C_{10}H_{15}OF_3$: C, 57.67; H, 7.25%. Found: C, 57.23; H, 7.36%.

(*E*)-1,1,1-Trifluoro-2-hydroxy-5-(4-methoxy)phenyl-3-propene (**5b**) was obtained according to the above typical procedure in 86% yield with traces of the *Z* isomer (GC).

^{1}H NMR δ: 3.31 (d, J=7.1 Hz, 2H); 3.72 (s, 3H); 4.35 (m, 1H); 5.45 (dd, J=7.0, 15.0 Hz, 1H); 6.01 (dt, J=7.1, 15.0 Hz, 1H); 6.75 (m, 2H); 6.98 (m, 2H) ppm. ^{13}C NMR δ: 37.8, 55.3, 71.3 (q, ^2J=32 Hz, *C*–CF_3); 114.1, 121.6, 126.2 (q, ^1J=280 Hz, CF_3); 127.6; 129.5; 130.9; 132.7; 137.6; 158.2 ppm. ^{19}F NMR δ: −79.5 (d, J=6.6 Hz) ppm. Analysis Calc. for $C_{11}H_{11}C_2F_3$: C, 56.89; H, 4.78%. Found: C, 57.31; H, 4.91%.

(*E*)-1,1,1-Trifluoro-2-hydroxy-4-phenyl-3-butene (**5d**) was obtained according to the above typical procedure in 85% yield with traces of the *Z* isomer (GC).

^{1}H NMR δ: 2.35 (bs, 1H); 4.55 (m, 1H); 6.12 (dd, J=7.0, 16.2 Hz, 1H); 5.92 (d, J=16.2 Hz, 1H); 6.85 (m, 1H); 6.95–7.58 (m, 9H) ppm. ^{13}C NMR δ: 71.5 (q, ^2J=32 Hz, *C*–CF_3); 123.5 (q, ^1J=284 Hz, CF_3); 126.8; 127.4; 128.5; 128.6; 129.3; 135.2; 136.2; 136.5 ppm. ^{19}F NMR δ: −79.3 (d, J=6.5 Hz) ppm. Analysis: Calc. for $C_{11}H_{11}OF_3$: C, 61.10; H, 5.14% Found: C, 60.71; H, 4.98%.

(*E*)-1,1,1-Trifluoro-2-hydroxy-5-phenyl-3-pentene (**5e**) was obtained according to the above typical procedure in 87% yield with traces of the *Z* isomer (GC).

^{1}H NMR δ: 3.49 (d, J=7.1 Hz, 2H); 4.42 (m, 1H); 5.61 (dd, J=7.0, 15.1 Hz, 1H); 6.19 (dt, J=7.1, 15.1 Hz, 1H); 7.18–7.62 (m, 5H) ppm. ^{13}C NMR δ: 35.5, 71.3 (q, ^2J=32 Hz, *C*–CF_3); 123.4, 124.3 (q, ^1J=282 Hz, CF_3); 126.3; 127.1; 127.5; 128.2; 136.6; 137.1; 138.8 ppm. ^{19}F NMR δ: −79.3 (d, J=6.6 Hz) ppm. Analysis: Calc. for $C_{10}H_9OF_3$: C, 59.40; H, 4.50%. Found: C, 59.58; H, 4.59%.

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